Remarks

1. Status of the Claims

Claims 1-37 were pending in this application of which Claim 12-19 and 27-37 were withdrawn from consideration. Without acquiescing to the Restriction Requirement, but to expedite prosecution and allowance, in this response, Claims 12-14 (Group II), Claim 27 (Group IV), Claims 18 and 19 (within Group III) and Claims 35-37 (within Group VI) have been canceled. Applicants reserve the right to protect the subject matter of the canceled claims in divisional applications. Accordingly, Claims 1-11, 15-17, 20-26, and 28-34 remain pending in this application.

2. Rejection of Claims 1-11 and 20-26 under 35 U.S.C. §103(a)

Claims 1-11 and 20-26 were again rejected under 35 U.S.C. §103(a) as being unpatentable over Moran et al. (US 6,576,793 B1). Applicants respectfully traverse the rejection for the following reasons.

In the previous Office Action, dated August 1, 2005, the Examiner cited *Ex parte Hartop* 139 USPQ 525 and *In re Cofer 148* USPQ 268 as the authority for his position that "crystalline form is no more than a different physical form of the compound, and a mere different physical nature of the compound is unpatentable, absent evidence to the contrary" (Office Action, page 2, lines 18-20).

As described in MPEP §2144.04 (VII.), the decision of *In re Cofer* supports the proposition that patentability depends on whether the prior art suggests the specific form of the claimed material and suitable methods to obtain the specific form. MPEP §2144.04 (VII.) specifically advises:

> Factors to be considered in determining whether a purified form of an old product is obvious over the prior art include whether the claimed chemical compound or composition has the same utility as closely related materials in the prior art, and whether the prior art suggests the particular form or structure of the claimed material or suitable methods of obtaining that form or structure. *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) (Claims to the free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals.) (emphasis added)

Thus, according to *In re Cofer*, when the prior art does not suggest the claimed compound in crystalline form and a process of obtaining such crystals, the claims are patentable over the prior art.

Applicants' Claim 1 recites "crystalline *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)-phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine dihydrochloride". The claim recites three distinct elements: the particular chemical compound, a particular salt of the compound, namely the dihydrochloride salt, and that the dihydrochloride salt of the compound be crystalline. Thus, in order to satisfy the criteria of *In re Cofer*, a prior art reference would have to suggest a crystalline dihydrochloride salt and a process of obtaining such crystals.

In Example 12, the cited reference discloses a synthetic route to prepare a free base racemic form of the compound of Claim 1. Applicants submit that nowhere does Moran '793 suggest a specific salt of the claimed compound nor any compound in crystalline form. Consequently, Moran '793 does not disclose a process for preparing the claimed crystalline dihydrochloride salt. Hence, according to *In re Cofer*, the present Claim 1 is patentable over Moran '793.

With respect to salt form, the Examiner has cited column 19 of the '793 patent. The cited column recites pharmaceutically-acceptable base addition salts (lines 4-42) and acid addition salts (lines 43-53). Specifically, at lines 43-53 of column 19, Moran '793 discloses:

> Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, napththoic acid, 2-hydroxynaphthoic acid, and the like.

Column 19 of the reference, however, does not disclose a dihydrochloride salt of the present compound; it merely discloses a list of possible salts that might be prepared for any of the many compounds disclosed in the reference. The mere disclosure of a list of possible salts in combination with a list of many compounds is not a specific disclosure of each salt of each compound.

Further, it is well known in the art that pharmaceutical agents do not form crystalline salts with every possible counterion and even in cases where such crystalline salts are possible, specific processes may be required for their formation. Numerous patents describing the necessary processes to prepare specific crystalline salts of pharmaceutical agents attest to this fact. Applicants respectfully submit, the Examiner has failed to explain how the mere recitation of known pharmaceutically acceptable salts suggests that the chemical compound of Claim 1 forms a crystalline hydrochloride salt with the specific claimed stoichiometry of a dihydrochloride salt.

With respect to crystalline form, the Examiner has cited column 35, line 34 of the reference. At column 35, lines 30-34, Moran '793 states:

> The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including, but not limited to filtration, distillation, crystallization, chromatography, and the like. (emphasis added)

Applicants respectfully submit that the disclosure that starting materials and intermediates may be purified by conventional techniques, among which crystallization is included, does not constitute a suggestion that the presently claimed dihydrochloride salt of *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)-phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine may be prepared in crystalline form nor does it suggest a process of preparation.

The Examiner has failed to show that Moran '793 suggests the claimed compound in crystalline form nor how to obtain such crystals. Therefore, Moran '793 does not meet the requirements articulated in *In re Cofer* for a reference to support an obviousness rejection and the rejection should be withdrawn.

For the same reasons the rejection does not meet the requirements as set forth in *In re Cofer* to support an obviousness rejection, the rejection does not meet the requirements as set forth in MPEP §2143 to establish a *prima facie* case of obviousness. First, there must be some suggestion to modify the reference. As described above, the reference does not suggest the dihydrochloride salt of the present chemical compound. The reference merely include hydrochloric acid among a list of acids that might be used to prepare salts of the compounds disclosed therein. The Examiner has failed to establish the motivation to modify the disclosure of the reference to select a dihydrochloride salt of the present compound.

Second, the Examiner must show that the proposed modification of the prior art had a reasonable expectation of success. The Examiner has not addressed the question of whether one skilled in the art would have had a reasonable expectation of success in obtaining a crystalline dihydrochloride salt of the present compound. It is well established in the pharmaceutical arts that the formation of crystalline salts is unpredictable. See, for example, *Handbook of Pharmaceutical Salts*, P. H. Stahl, C. G. Wermuth, Eds., Verlag, Helvetica Chimica Acta, Zurich (2002), p. 137, 6th paragraph) ("No predictive procedure to determine whether a particular acidic or basic drug would form a salt with a particular counter-ion has been reported in the literature."). In view of the unpredictability of the art, and the Examiner's failure to explain how one of ordinary skill would have had a reasonable expectation of obtaining a crystalline dihydrochloride salt of the compound, the Examiner has not met the burden of establishing a reasonable expectation of success. (See MPEP § 2143.02 Reasonable Expectation of Success is Required) Thus, a *prima facie* case of obviousness has not been established and for this reason, as well, the rejection should be withdrawn.

In view of the foregoing, independent Claims 1 and 7 and Claims 2-6 and 8-11 dependent from Claim 1 are patentable over Moran '793. Claims 2-7 recite specific characteristics of the crystalline dihydrochloride salt of Claim 1. Since the reference does not suggest the claimed compound in crystalline form nor how to obtain such crystals, it certainly does not suggest a crystalline compound with the specific x-ray powder diffraction pattern recited in Claims 2-4 and 7, the infrared absorption spectrum of Claim 5, nor the differential scanning calorimetry characteristic of Claim 6. For these additional reasons, as well, Claims 2-7 are patentable over Moran '793.

Applicants have additionally pointed out that secondary considerations support the patentability of Claims 1-11. For example, at page 6, lines 15-26, the present specification provides evidence of the particular advantages of the presently claimed material for the preparation of pharmaceutical formulations for administration by inhalation. The Examiner has failed to take this evidence into consideration arguing, "[t]here is no side-by-side comparison and hence no unexpected results noted.". Applicants respectfully submit, the Examiner is improperly imposing a requirement for a side-by-side comparison, essentially requiring that some inferior material be described in the specification in order for the secondary evidence to be considered.

It is well known that some solid salt forms of pharmaceutical compounds are hygroscopic or deliquescent or that they degrade upon storage. There can be no *a priori* assumption that an arbitrary crystalline form will have the desirable properties described for the present material. Hence, Applicants respectfully submit the objective evidence, as presented, should be taken into consideration in support of the patentability of Claims 1-11.

Claims 20-26 recite a pharmaceutical composition comprising *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine dihydrochloride; a buffering agent; and water; wherein the buffering agent is present in an amount sufficient to provide the composition with a pH in the range of between about 4 and about 6. The Office Actions in this application have been silent with respect to the subject matter of Claims 20-26.

Moran '793 does not teach or suggest a pharmaceutical composition with the limitations of Claim 20 and claims dependent therefrom. The Examiner has failed to establish a *prima facie* case of obviousness for Claims 20-26 based on Moran '793.

Furthermore, at page 9, lines 9-16, the specification provides objective evidence of the unexpected benefits of a pharmaceutical composition according to Claims 20-26, namely evidence of the stability of the pharmaceutical composition of Claims 20-26 upon storage. In contrast, U.S. 6,040,344 identified stability of a pharmaceutical composition of formoterol tartrate, a different β_2 adrenergic receptor agonist, prepared for the same form of administration, as a limitation to its acceptability. Consideration of the present evidence of unexpected results, further supports the patentability of Claims 20-26.

In summary, Claims 1-11 and 20-26 have been shown to be unobvious and patentable over Moran '793. Accordingly, the present rejection of Claims 1-11 and 20-26 under 35 U.S.C. §103(a) should be withdrawn.

3. Conclusion

In view of the foregoing, Applicants respectfully submit Claims 1-11 and 20-26 are in condition for allowance. Further, upon allowance, according to *In re Ochiai* (71F. 3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and MPEP §821.04, the restriction between Group I and Groups III (pending Claims 15-17) and V (Claims 28-30), both of which are process claims, and between Group I and Group VI (pending Claims 31-34), which are method of use claims, may be withdrawn. Reconsideration of this application and prompt passage to allowance is respectfully requested. Should there be any issues regarding this application that may be resolved by telephone, the examiner is invited to telephone the undersigned agent for Applicants at (650) 808-3764 (direct).

Respectfully submitted,
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